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IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICUS CURIAE* WYETH IN SUPPORT OF PETITIONER

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TABLE OF CONTENTS

Page

TABLE OF CONTENTS i

TABLE OF AUTHORITIES ii

INTEREST OF AMICUS CURIAE 1

SUMMARY OF ARGUMENT 2

ARGUMENT 2

I. THE DECISION BELOW CONFLICTS WITH THIS COURT'S PRECEDENT 2

II. THE SAFE HARBOR PROVISION OF SECTION 271(e)(1) APPLIES TO PRECLINICAL STUDIES 5

III. THE LACK OF ANY MEANINGFUL COMMON LAW EXCEPTION FOR RESEARCH MAKES THE SAFE HARBOR PROTECTIONS VITAL 11

IV. ANY NARROWING OF THE SECTION 271(e)(1) SAFE HARBOR WILL REDUCE DRUG RESEARCH AND DEVELOPMENT IN THE UNITED STATES 12

CONCLUSION 14

TABLE OF AUTHORITIES

Page

CASES

Bayer AG v. Elan Pharmaceutical Research Corp., 212 F.3d 1241 (Fed. Cir. 2000) 6
Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661 (1990) 2, 3
Integra Lifesciences I Ltd., et al. v. Merck KGaA, 331 F.3d 860 (Fed. Cir.), *reh'g denied*, (Fed. Cir. Dec. 3, 2003) ..... *passim*
Madey v. Duke University, 307 F.3d 1351 (Fed. Cir. 2002), *cert. denied*, 123 S. Ct. 2639 (2003) 11
Public Citizen Health Research Group v. Food & Drug Admin., 185 F.3d 898 (D.C. Cir. 1999) 6

REGULATIONS AND STATUTES

21 C.F.R. Part 58 9
21 C.F.R. § 312.23 7
21 C.F.R. § 312.23(a)(8) 8
21 C.F.R. § 312.33 9
21 C.F.R. § 312.33(a)(6) 10
21 C.F.R. § 312.42 7
21 C.F.R. § 314.50(d)(2)(ii) 10
21 U.S.C. § 355(i) 6
21 U.S.C. § 355(i)(1)(A) 6, 7
35 U.S.C. § 271(e)(1) ..... *passim*

TABLE OF AUTHORITIES – Continued

Page

LEGISLATIVE MATERIALS AND OTHER SOURCES

H.R. Rep. No. 98-857 (Pt. 1) (1984) 4
Pharmaceutical Research and Manufacturers of America ("PhRMA") Industry Profile 2003, *available at* www.phrma.org/publications/publications/profile02/Index.cfm 12

INTEREST OF AMICUS CURIAE[1]

Wyeth is one of the world's largest research-driven pharmaceutical and health care companies. Wyeth's business centers around discovering, developing, testing, and bringing to market new drugs and new methods of using drugs. As part of that business, Wyeth has submitted dozens of applications to the FDA for investigational use and marketing approval of new drugs. Last year alone, Wyeth filed fourteen applications for investigational use, directed to a wide range of treatments for dreaded diseases and conditions. Wyeth also has obtained hundreds of patents, including patents covering basic compounds and research methods.

Wyeth has no financial interest in the parties to this litigation or in the outcome of this specific case, other than its interest in seeking a correct and consistent interpretation of 35 U.S.C. § 271(e)(1). That interest leads Wyeth to support the petition by Merck KGaA, seeking review of the decision of the court below. Any narrowing of the safe harbor provision will seriously harm drug research and development activities in the United States. Accordingly, Wyeth submits that this Court should grant the Petition for Writ of Certiorari of Merck KGaA and protect drug development activities in the United States - the very backbone of the pharmaceutical industry.

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[1] This brief was not authored, in whole or in part, by counsel for either party. No person or entity other than the *amicus curiae* and their counsel contributed to the preparation or submission of the brief. The parties consented to the filing of the brief and copies of their letters of consent have been lodged with the Clerk of the Court.

SUMMARY OF ARGUMENT

The erroneous decision of the Court of Appeals in *Integra Lifesciences I Ltd., et al. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir.), *reh'g denied,* (Fed. Cir. Dec. 3, 2003), will have far reaching, adverse consequences to the innovator pharmaceutical industry, including Wyeth. Until now, consistent with the literal language of the statute and this Court's precedent, the safe harbor provision of 35 U.S.C. § 271(e)(1) has been construed broadly.

As a result of the decision below, the tangible benefits of the safe harbor may be rendered ephemeral -- providing protections from infringement actions to late stage clinical trials but leaving exposed prerequisite developmental work necessary to get to that stage. Because the Food and Drug Administration's (FDA's) regulations require that extensive developmental work be undertaken before late stage clinical trials may even commence, such developmental work must come within the safe harbor of § 271(e)(1).

If left unchanged, the restrictive majority decision will deprive pharmaceutical companies of the full scope of the § 271(e)(1) exemption. As a consequence of the restrictive ruling of the Court of Appeals, research and development activities in the United States directed to new drugs will be significantly diminished.

ARGUMENT

I. THE DECISION BELOW CONFLICTS WITH THIS COURT'S PRECEDENT

This Court's decision in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990), interpreted § 271(e)(1) broadly to

apply to the *entire* FDA statutory scheme of regulation, not merely a specific narrow subsection of federal law. *Eli Lilly*, 496 U.S. at 666-70. In concluding that medical devices -- although not specifically mentioned in § 271(e)(1) -- qualify for the protections of the statute, this Court focused on the broad language and purposes of the statute itself, which clearly encompass more than activities related to the filing of applications for approval of generic drugs. *Eli Lilly*, 496 U.S. at 666-70.

Under this Court's interpretation in *Eli Lilly*, there can be no doubt that the *entire* FDA approval process for new drugs constitutes a "Federal law which regulates the manufacture, use, or sale of drugs . . .". § 271(e)(1). Consequently, the decision in *Eli Lilly* requires that activities "reasonably related" to acquiring approval of a new drug -- including required underlying developmental work and animal testing -- come within the ambit of § 271(e)(1). This Court's expansive interpretation of the statute in *Eli Lilly* makes the restrictive decision of the court below all the more surprising.

Any narrowing of § 271(e)(1) risks defeating the fundamental purposes set out for the exemption: permitting companies to develop information for submission to the FDA, without fear of patent infringement actions. Any artificial line that excludes early testing, such as preclinical testing, will have drastic adverse effects on research in the pharmaceutical industry.

The court below acknowledges that § 271(e)(1) protects clinical trials performed on drug products. It also acknowledges that such protections are not limited to so-called "generic" drug products. However, it would be contrary to the statute to arbitrarily limit the exemption only

to "clinical trials." Rather, the statute protects activity "solely for uses reasonably related to" development and submission of information to the FDA under the Federal Food, Drug, and Cosmetic Act (FDCA). Moreover, information need not actually be submitted to the FDA in order for a drug developer to qualify for the safe harbor protections. In that regard, the legislative history of § 271(e)(1) clearly provides:

> A party which develops such information, *but decides not to submit an application for approval*, is protected as long as the development was done *to determine whether or not an application for approval would be sought.*

H.R. Rep. No. 98-857 (Pt. 1), at 45 (1984) (emphasis added).

The FDCA and FDA regulations specify the many kinds of information that the FDA expects pharmaceutical companies to generate and submit to the agency. These kinds of information are required to ensure that drug products used in humans are safe, effective, and produced under appropriate quality standards. Generation of such information requires the use of compounds or methods in ways that, without an exemption, could be considered infringing. However, the use of such compounds or methods was expressly authorized by Congress when it enacted § 271(e)(1). Thus, the fears of the majority of the Court below that § 271(e)(1) -- if not construed narrowly -- "would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions," *Integra*, 331 F.3d at 867, are unwarranted.

In the decision below, the court characterized drug development work as encompassing experiments to evaluate

the specificity, efficacy, and toxicity of new drugs and to determine which were effective and safe enough to warrant further testing in humans. *Integra*, 331 F.3d at 863. Indeed, as the dissent points out, such development work ultimately led to the filing of an Investigational New Drug Application (IND) with the FDA. *Id.* at 874. If these early drug development activities were to be outside the protections of the safe harbor, drug innovators would be caught in a Catch-22 situation. Innovators would be afforded a safe harbor only for late-stage drug approval activities; but earlier drug development experiments could be stopped dead in their tracks, preventing an innovator from ever reaching the safe harbor. That anomalous result could not possibly be the intent of the statute.

II. THE SAFE HARBOR PROVISION OF SECTION 271(e)(1) APPLIES TO PRECLINICAL STUDIES

What is necessarily included in the safe harbor extends, of course, beyond just the clinical trials themselves. There are numerous activities directly related to conducting clinical trials which must be included, such as manufacturing a new drug, and distributing it to the clinical investigators who administer the drug and measure the safety and efficacy of the drug in the clinical subjects.

Likewise, preclinical tests (including animal studies) also are required by the FDA and must by definition come within the scope of the safe harbor. Preclinical testing is not far removed from the actual FDA approval process. Rather, preclinical testing is expressly ***required*** under federal law as a necessary predicate to obtaining approval to conduct

human clinical trials.[2] Thus, preclinical testing required to seek approval to conduct clinical trials also must be covered by the safe harbor.

Indeed, *any* other types of testing or information *required* by the FDA must automatically be covered by § 271(e)(1). *See Bayer AG v. Elan Pharmaceutical Research Corp.*, 212 F.3d 1241, 1249 (Fed. Cir. 2000) (activities "required" by the FDA approval process are exempt under the safe harbor of § 271(e)(1)). Nothing in § 271(e)(1), nor the legislative history, excludes drug development activities and animal tests from the protection of the statute. On the contrary, the "reasonably related" language in the statute necessarily embraces a wide range of drug development activities.

An understanding of the FDA requirements also bolsters this conclusion. Applicants for marketing approval of new drug products must submit New Drug Applications (NDAs) to the FDA. NDAs must include reports of clinical investigations performed on humans that demonstrate that the product is safe and effective.

To protect human subjects, new drug developers cannot perform clinical studies on a research drug in humans until they submit to the FDA an IND and the IND becomes effective.[3] The FDA will not allow an IND to become

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[2] *See* 21 U.S.C. § 355(i)(1)(A) (authorizing the FDA to require "preclinical tests (including tests on animals)" as a predicate to allowing clinical testing in humans); *see also Public Citizen Health Research Group v. Food & Drug Admin.*, 185 F.3d 898, 901 (D.C. Cir. 1999).

[3] 21 U.S.C. § 355(i).

effective unless it is convinced that the drug does not pose a significant health risk to humans. If not convinced, the FDA can impose a hold on the clinical study.[4]

The FDA reviews the various information submitted in the IND to make its decision about whether a clinical trial may proceed. The FDCA states that the FDA regulations govern the content of INDs, and that an IND must include "preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing."[5] Although there is some variation from drug to drug, the core of an IND contains an explanation of the chemical and physical characterization of the drug, and a demonstration by means of the results of tests conducted in vitro or in animals that the drug is appropriate for use in subsequent tests in humans. FDA regulations require that an applicant include at least the following information in an IND:[6]

1. An introductory statement and general investigational plan;

2. An Investigator's Brochure containing, among other things, a description of the drug, *a summary of the pharmacological and toxicological effects of the drug in animals* (and humans, if known), and *a summary of the pharmacokinetics and biological disposition of the drug in animals* (and humans, if known);

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[4] 21 C.F.R. § 312.42.

[5] 21 U.S.C. § 355(i)(1)(A).

[6] 21 C.F.R. § 312.23.

3. Protocols for the proposed clinical trials;

4. Chemistry, manufacturing, and control information;

5. Pharmacology and toxicology information; and

6. Relevant human experience and other specific information.

Pharmaceutical companies must submit this information to the FDA to receive permission to go forward with subsequent clinical trials, which in turn must be submitted in order to gain final approval to market the drug.

Consequently, it is contrary to the safe harbor provision to categorically exclude data required to be generated, and submitted to the FDA, in support of an application. *All* of the underlying work performed to generate that data is necessarily for "uses reasonably related to" seeking market approval.

At the very least, animal tests must fall squarely within the safe harbor. The FDA regulations for an IND require that the IND must contain:[7]

> *Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals* or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical

[7] 21 C.F.R. § 312.23(a)(8) (emphasis added).

> investigations. *The kind, duration, and scope of animal* and other *tests* required varies with the duration and nature of the proposed clinical investigations....
>
> *(a) An integrated summary of the toxicological effects of the drug in animals* and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

Thus, the FDA clearly requires preclinical testing, including in vitro and animal testing. In addition, the FDA requires certain preclinical tests to be conducted in accordance with the FDA's Good Laboratory Practice regulations,[8] which are designed to ensure the quality of the studies that form the basis for the application.

[8] 21 C.F.R. Part 58.

Animal and in vitro testing is not only conducted prior to clinical tests. For example, the FDA also requires that pharmaceutical companies submit annual reports on the progress of IND investigations.[9] Such reports must include:

> A list of the preclinical studies (*including animal studies*) completed or in progress during the past year and a summary of the major preclinical findings.[10]

Animal and in vitro testing is also required by the FDA as part of an NDA. For example, the FDA requires pharmaceutical companies to conduct long-term toxicology studies to assess carcinogenicity. Such studies often are conducted at the same time as clinical trials and are submitted with the NDA. FDA regulations thus require NDAs to contain a section describing "animal and in vitro studies with the drug," including: "Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use."[11] All of these studies are in the body of data FDA considers in approving a drug.

Given this Court's decision in *Eli Lilly, all* of the studies just discussed are "reasonably related to" the

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9 21 C.F.R. § 312.33.

10 21 C.F.R. § 312.33(a)(6) (emphasis added).

11 21 C.F.R. § 314.50(d)(2)(ii).

development and submission of information to the FDA. There is no justification for excluding *required* preclinical development and animal tests from the protection of § 271(e)(1).

III. THE LACK OF ANY MEANINGFUL COMMON LAW EXCEPTION FOR RESEARCH MAKES THE SAFE HARBOR PROTECTIONS VITAL

As pointed out by the dissent below:

> the patent system both contemplates and facilitates research into patented subject matter, whether the purpose is scientific understanding or evaluation or comparison or improvement. Such activities are integral to the advance of technology.

Integra, 331 F.3d at 875. Consistent with this principle, many other countries have recognized a research exemption from patent infringement actions. Here in the United States, however, the common law research exemption has been shrunken to the point of virtual nonexistence. Presently, the research exemption in the United States applies only to acts performed solely "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry." *Madey v. Duke University*, 307 F.3d 1351, 1362 (Fed. Cir. 2002), *cert. denied*, 123 S. Ct. 2639 (2003). Work that is in "any way commercial in nature" -- even at major research universities such as Duke -- does not qualify for the research exemption. *Id.*

Given the lack of any viable common law research exemption from patent infringement actions, the statutory exemption created by Congress with the safe harbor under

§ 271(e)(1) is of paramount importance to the pharmaceutical industry. Shrinking this statutory protection would leave drug innovators with no alternative protections for research and development activities designed to discover and bring to market new drugs.

IV. ANY NARROWING OF THE SECTION 271(e)(1) SAFE HARBOR WILL REDUCE DRUG RESEARCH AND DEVELOPMENT IN THE UNITED STATES

The stakes are high here. If § 271(e)(1) is construed to exclude preclinical testing of new drugs, the resulting increased risk of patent infringement actions will chill the pharmaceutical industry's incentive to conduct new drug research and development in the United States. Large categories of activities previously thought to have been covered by the safe harbor could now apparently be open to infringement attacks. As a result of the decision below, an imbalance now exists between the United States and many foreign countries in the scope of available exemption from infringement for research and development, including new drug development activities. This imbalance will likely influence companies to outsource new drug development abroad, creating a reverse-flow of money, jobs, and new technology out of the United States. In addition, foreign-based pharmaceutical companies will no doubt balk at continuing and expanding their new drug development activities in the United States.

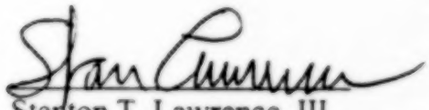
These effects are significant because the innovator pharmaceutical industry is more than just a source for valuable medicines that improve the health and well-being of the public. This vigorous industry is one of the key drivers of growth for the United States economy. Due to the size

and significance of the innovator pharmaceutical industry, even a small reduction in drug research and development in the United States will have enormous consequences. In 2002, innovator drug manufacturers spent an estimated $32 billion on research and development, and more than 80% of that within the United States. *See* Pharmaceutical Research and Manufacturers of America ("PhRMA") Industry Profile 2003 at 10 (available online at www.phrma.org/publications/publications/profile02/Index.cfm). In 2003, Wyeth invested nearly $2.1 billion in research and development and filed fourteen applications in the FDA to begin clinical trials on therapies for Alzheimer's disease, cancer, hepatitis C, neuropathic pain, thrombosis and other significant conditions. The innovator pharmaceutical industry is also one of this country's largest employers, with approximately 223,000 employees nationwide. PhRMA Industry Profile at 17. The human and social costs resulting from the decision below, including the loss of substantial revenue and thousands of jobs, could be very significant. The dissent in the court below had it right: the "change of law [by the majority] is ill-suited to today's research-founded, technology-based economy." *Integra*, 331 F.3d at 873.

CONCLUSION

For the foregoing reasons, Wyeth respectfully requests that this Court grant Merck KGaA's Petition for Writ of Certiorari. Moreover, because the decision of the Court of Appeals so clearly departs from this Court's precedent, the plain language of the statute and sound policy, that decision should be reversed.

Respectfully submitted,



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